In vitro safety "clinical trial" of the cardiac liability of drug polytherapy.

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Funding Grants: Human Cardiac Chip for Assessment of Proarrhythmic Risk , Safety “Clinical Trial” of the Cardiac Liability of COVID19 Polytherapy

Public Summary:

Scientific Abstract:
Only a handful of US Food and Drug Administration (FDA) Emergency Use Authorizations exist for drug and biologic therapeutics that treat severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) infection. Potential therapeutics include repurposed drugs, some with cardiac liabilities. We report on a chronic preclinical drug screening platform, a cardiac microphysiological system (MPS), to assess cardiotoxicity associated with repurposed hydroxychloroquine (HCQ) and azithromycin (AZM) polytherapy in a mock phase I safety clinical trial. The MPS contained human heart muscle derived from induced pluripotent stem cells. The effect of drug response was measured using outputs that correlate with clinical measurements, such as QT interval (action potential duration) and drug-biomarker pairing. Chronic exposure (10 days) of heart muscle to HCQ alone elicited early afterdepolarizations and increased QT interval past 5 days. AZM alone elicited an increase in QT interval from day 7 onward, and arrhythmias were observed at days 8 and 10. Monotherapy results mimicked clinical trial outcomes. Upon chronic exposure to HCQ and AZM polytherapy, we observed an increase in QT interval on days 4-8. Interestingly, a decrease in arrhythmias and instabilities was observed in polytherapy relative to monotherapy, in concordance with published clinical trials. Biomarkers, most of them measurable in patients' serum, were identified for negative effects of monotherapy or polytherapy on tissue contractile function, morphology, and antioxidant protection. The cardiac MPS correctly predicted clinical arrhythmias associated with QT prolongation and rhythm instabilities. This high content system can help clinicians design their trials, rapidly project cardiac outcomes, and define new monitoring biomarkers to accelerate access of patients to safe coronavirus disease 2019 (COVID-19) therapeutics.